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SARS-CoV-2 Vaccine-Induced Immune Responses Among Hematopoietic Stem Cell Transplant Recipients

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Background. Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination reduces the risk and severity of coronavirus disease 2019 (COVID-19), several variables may impact the humoral response among patients undergoing hematopoietic stem cell transplantation (HSCT).

Methods. A retrospective chart review was conducted among SARS-CoV-2-vaccinated HSCT recipients between 2020 and 2022 at a single center in Boston, Massachusetts. Patients age ≥18 years who received doses of Pfizer, Moderna, or J&J vaccines were included. Anti-spike (S) immunoglobulin G (IgG) titer levels were measured using the Roche assay. Responders (≥0.8 U/mL) and nonresponders (<0.8 U/mL) were categorized and analyzed. Multivariable linear and logistic regression were used to estimate the correlation coefficient and odds ratio of response magnitude and status.

Results. Of 152 HSCT recipients, 141 (92.8%) were responders, with a median (interquartile range [IQR]) anti-S IgG titer of 2500 (107.9–2500) U/mL at a median (IQR) of 80.5 (36–153.5) days from last dose, regardless of the number of doses received. Higher quantitative titers were associated with receipt of more vaccine doses (coeff, 205.79; 95% CI, 30.10 to 381.47; $P = .022$), being female (coeff, 343.5; 95% CI, −682.6 to −4.4; $P = .047$), being younger (<65 years; coeff, 365.2; 95% CI, −711.3 to 19.1; $P = .039$), and not being on anti-CD20 therapy (coeff, −1163.7; 95% CI, −1717.7 to −609.7; $P = .001$). Being male (odds ratio [OR], 0.11; 95% CI, 0.01 to 0.93; $P = .04$) and being on anti-CD20 therapy (OR, 0.16; 95% CI, 0.03 to 0.70; $P = .016$) were associated with nonresponse.

Conclusions. Overall, most HSCT recipients had high SARS-CoV-2 antibody responses. More vaccine doses improved the magnitude of immune responses. Anti-S IgG monitoring may be useful for identifying attenuated vaccine-induced responses.

Keywords. COVID-19 vaccine; allogeneic HSCT; antispike protein; autologous HSCT transplant.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination reduces the risk and severity of coronavirus disease 2019 (COVID-19) [1–3], but immunogenicity has been found to be reduced in patients with hematologic malignancies [4] and those undergoing hematopoietic stem cell transplantation (HSCT) [5]. HSCT recipients undergo various degrees of disease-related and therapeutic immunosuppression that may compromise their ability to produce an effective immune response and therefore increase their vulnerability to infections. The variables that may impact the humoral response, such as age, gender, pretransplant diagnosis, transplant type, prior treatments, and vaccine type and number, have not been comprehensively described.

Before the Food and Drug Administration (FDA)–authorized use of SARS-CoV-2 vaccines, transplant patients had a significantly higher mortality rate compared with healthy adults after infection with SARS-CoV-2 [6]. The pivotal clinical trials that led to the accelerated authorization of the SARS-CoV-2 vaccines were conducted among healthy participants [1, 2]. Immunocompromised patients, including HSCT recipients, were excluded from the phase 3 COVID-19 vaccine trials despite their uniquely higher risks of severe infection and death [7–10].

Several studies have demonstrated relatively poor SARS-CoV-2 vaccine immune responses among HSCT recipients following vaccination as compared with healthy adults. Sherman et al. and Mamez separately reported suboptimal antibody titers with a seropositivity prevalence of ~80% among HSCT recipients when compared with healthy adults [11–14]. Before the recommendation for booster dose vaccinations, certain

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factors had been linked to poor sero-responsiveness including time post-transplant, presence or absence of graft-vs-host disease (GVHD), and use of anti-CD20 therapies [15, 16]. Medications such as methotrexate, sirolimus, high-dose steroids, and mycophenolate mofetil commonly used in the management of GVHD among HSCT recipients have been implicated in poor SARS-CoV-2 vaccine immunogenicity among solid organ transplant recipients [2, 5, 6, 8, 17]. In other vaccine studies (eg, with the influenza vaccine), the appropriate timing of vaccination affected immunogenicity among HSCT recipients [18].

Given the heightened risk of death and severe disease following infection with SARS-CoV-2, knowledge of SARS-CoV-2 vaccine responsiveness remains pertinent in addressing the unique needs of HSCT recipients. The goal of our study was to determine the prevalence of seropositivity and magnitude of anti-spike (S) immunoglobulin G (IgG) after SARS-CoV-2 vaccination in HSCT recipients and determine factors associated with seropositivity in this population. Insights gained from this study may aid in the development of improved vaccination strategies against SARS-CoV-2.

METHODS

Study Population

A single-center, retrospective review of electronic medical record (EMR) data was conducted among HSCT recipients who received SARS-CoV-2 vaccinations between January 2020 and August 2022 at Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston, Massachusetts. Patients were included if they were ≥18 years old and had received ≥1 dose of BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), or Ad26.COV2.S (Janssen) vaccine and had been tested at least once for anti-S IgG. Vaccines were administered intramuscularly according to their respective Emergency Use Authorizations (EUAs): BNT162b2 (30 mcg in 0.3 mL for all doses), mRNA-1273 (100 mcg in 0.5 mL for primary series, 50 mcg in 0.25 mL for booster doses), Ad26.COV2.S (5×10^{10} viral particles in 0.5 mL for all doses). All vaccines consisted of the monovalent ancestral SARS-CoV-2 spike sequence as the study period ended before the availability of bivalent variant-containing boosters. The anti-S IgG measurements occurred between January 28, 2021, and August 25, 2022. Patients were censored as of the date of SARS-CoV-2 monoclonal antibody (mAb) therapy or positive test for SARS-CoV-2 infection. Those who had anti-S IgG assays only before transplant or who relapsed and received an alternate treatment were excluded.

Patient Consent

This study was approved by the Mass General Brigham Institutional Review Board, which deemed that it was exempt from requiring participant informed consent.

Study Design

Anti-S IgG titers were quantitatively measured at the provider's discretion during routine care using the Roche Elecsys Anti-SARS-CoV-2 spike immunoassay. The assay has a cutoff defined by the manufacturer as ≥0.8 U/mL. Values below this were imputed to 0.4 U/mL; values above this were considered reactive (responder), while values below were considered nonreactive (nonresponder) [19]. Earlier anti-S IgG assays had a maximum reported titer of 2500 U/mL, while later assays had a higher maximum titer of 12 500 U/mL. For the later assays with titers >2500 U/mL, a different dilutional method was used in the lab. To ensure uniformity in reporting and facilitate appropriate comparisons, all anti-S IgG titers were adjusted to a maximum of 2500 U/mL before our analysis. Baseline demographic data, blood cell counts (CD4, WBC), and IgG levels were extracted from the EMR (starting 3 months before the first vaccination). The pretransplant conditioning regimen, type of transplant, GVHD prophylaxis, acute and chronic GVHD treatment, SARS-CoV-2 PCR result, COVID-19 treatment status, and type of vaccine received were extracted from the EMR. The study timeline for each eligible participant spanned between 3 months before the first dose of SARS-CoV-2 vaccination and the date of their last anti-S IgG antibody assay. To determine the time from the last vaccine dose after transplant, we used the results of the anti-S IgG assay that were collected after the last dose for all patient groups.

Statistical Analysis

Patients were categorized based on the number of doses of the vaccine(s) received before their last anti-S IgG titer. We analyzed these data using descriptive statistics to assess the quantitative difference in anti-S IgG titer and a Kruskal-Wallis or Mann-Whitney *U* test to assess for statistical significance between groups. Univariable and multivariable models were used to assess the relationship between key patient demographics, vaccine and treatment characteristics, and their association with vaccine response among HSCT recipients. A logistic regression model was used to calculate odds ratios (ORs) and 95% CIs for factors potentially associated with a dichotomous response status to SARS-CoV-2 vaccination (responders vs nonresponders). *P* values ≤.05 were considered statistically significant. Only variables with *P* values ≤.25 and certain clinically relevant variables regardless of statistical significance were included in the multivariable analysis. Factors evaluated included age, sex, neutrophil count, lymphocyte count, platelet counts, IgG level, prophylaxis and treatment for GVHD (eg, mycophenolate mofetil, sirolimus, systemic corticosteroids [≥20 mg], tacrolimus, and cyclophosphamide), receipt of anti-CD20 therapy (eg, rituximab, ocrelizumab, veltuzumab, obinutuzumab), type of transplant, type of conditioning regimen, time from transplant to first vaccination, time from first vaccination to first anti-S IgG titer assay, time from last dose to last antibody titer, and number of vaccine

Table 1. Demographic, Treatment, and SARS-CoV-2 Vaccination Characteristics of Hematopoietic Stem Cell Transplant Recipients

		Responders (n = 141)	Nonresponders (n = 11)	
	Total (n = 152)	Anti-S IgG Antibody ≥0.8 U/mL	Anti-S IgG Antibody <0.8 U/mL	*P* Value
Demographic characteristics				
Age, median (IQR), y	62 (50–68)	62 (50–68)	65 (36–68)	.57
Sex				**.011**
Female	70 (46.1)	69 (48.9)	1 (9.1)	
Male	82 (53.9)	72 (51.1)	10 (90.9)	
Race				.24
Non-White	13 (8.6)	11 (7.8)	2 (18.2)	
White	139 (91.5)	130 (92.2)	9 (81.8)	
Clinical characteristics				
Disease type				.32
AML/other acute leukemias	41 (27)	38 (27.0)	3 (27.3)	
CML/other chronic leukemias	9 (5.9)	8 (5.7)	1 (9.1)	
ALL	15 (9.9)	14 (9.9)	1 (9.1)	
Lymphomas (HL/NHL)	26 (17.1)	23 (16.3)	3 (27.3)	
Anemias/hemoglobinopathies	8 (5.3)	6 (4.3)	2 (18.2)	
Myelodysplastic Syndrome/myelofibrosis	41 (27)	40 (28.4)	1 (9.1)	
Multiple myelomas	12 (7.9)	12 (8.5)	0 (0.0)	
Baseline WBC count, median (IQR), cells × 10^9/L	4.6 (3.5–6.0)	4.7 (3.5–6.0)	4.6 (3.2–6.2)	.72
Baseline lymphocyte count, median (IQR), cells × 10^9/L	1 (0.6–1.5)	1 (0.6–1.5)	1 (0.8–1.1)	.34
Baseline CD_4 lymphocyte count, median (IQR), cells × 10^6/L	281.5 (183–405)	305.5 (183–420)	225 (171–324)	.45
Baseline IgG level, median (IQR), mg/dL	652 (498.5–1020.5)	652 (507–1023)	436 (367–756)	.18
Preparation intensity				.74
Myeloablative	63 (41.5)	59 (41.8)	4 (36.4)	
Nonmyeloablative	7 (4.6)	6 (4.3)	1 (9.1)	
Reduced-intensity conditioning	82 (54)	76 (53.9)	6 (54.5)	
Transplant type				.43
Autologous	28 (18.4)	25 (17.7)	3 (27.3)	
Allogeneic	124 (81.6)	116 (82.3)	8 (72.7)	
Acute GVHD				.62
Yes	32 (15.5)	21 (15.9)	1 (10)	
No	120 (84.5)	111 (84.1)	9 (90)	
Chronic GVHD				.57
Yes	57 (37.5)	52 (36.9)	5 (45.5)	
No	95 (62.5)	89 (63.1)	6 (54.5)	
Pharmacotherapy around the time of vaccination				
GVHD prophylaxis (tacrolimus)				**<.001**
Yes	77 (50.7)	77 (54.6)	0 (0)	
No	75 (49.3)	64 (45.4)	11 (100)	
Acute GVHD treatment (tacrolimus)				.73
Yes	10 (6.6)	9 (6.4)	1 (9.1)	
No	142 (93.4)	132 (93.6)	10 (90.9)	
Chronic GVHD treatment (tacrolimus)				.66
Yes	36 (23.7)	34 (24.1)	2 (18.2)	
No	116 (76.3)	107 (75.9)	9 (81.8)	
Systemic corticosteroids				.85
Yes	65 (42.8)	60 (42.6)	5 (45.5)	
No	87 (57.2)	81 (57.4)	6 (54.5)	
Anti-CD20 therapy				**.004**
Yes	16 (10.5)	12 (8.5)	4 (36.4)	
No	136 (89.5)	129 (91.5)	7 (63.6)	
Vaccination characteristics				
Time from transplant to first vaccine dose, median (IQR),[a] d	140.5 (−48 to 254)	136 (−56 to 253)	217 (174–330)	.096
No. of vaccine doses				.28
1	11 (7.8)	11 (0)	0 (0)	
2	66 (44.0)	62 (31.9)	4 (27.3)	
3	55 (34.0)	48 (44.7)	7 (72.7)	

Table 1. Continued

		Responders (n = 141)	Nonresponders (n = 11)	
	Total (n = 152)	Anti-S IgG Antibody ≥0.8 U/mL	Anti-S IgG Antibody <0.8 U/mL	*P* Value
4	10 (7.1)	10 (7.8)	0 (0)	
5	10 (7.1)	10 (11.3)	0(0)	

P values ≤ .05 are indicated in boldface.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; GVHD, graft-vs-host disease; HL, Hodgkin lymphoma; IQR, interquartile range; NHL, non-Hodgkin lymphoma; WBC, white blood cells.

[a]Negative time means patient had first vaccine dose before transplant.

doses received. Stata, version 17.0, and GraphPad Prism 9 were used to analyze the study data and render figures.

RESULTS

Sociodemographic Characteristics and Magnitude of Antispike Response

A total of 871 HSCT recipients were screened, and 152 patient records met the study inclusion criteria (Supplementary Figure 1). Of these, 82 (54%) were male, and the median age (interquartile range [IQR]) was 62 (50–68.0) years. Participants were predominantly White (n = 139, 91.5%). The majority of patients, 124 (81.6%), received an allogeneic transplant, and 28 (18.4%) received an autologous transplant. Patients received anywhere from 1 to 5 SARS-CoV-2 vaccinations, with most patients receiving ≥3 vaccines (98/152, 64.5%) (Supplementary Table 1). Other characteristics such as underlying disease, preparation intensity, transplant type, and medications used in the prophylaxis and treatment of acute and chronic GVHD are described in Table 1.

Descriptive Analysis Comparing Anti-S IgG Levels in Various Categories

The results comparing anti-S IgG titers between HSCT recipients stratified by number of vaccines received are shown in Figure 1. In addition, there was no statistically significant difference in the anti-S IgG assay time between the different patient strata (Figure 1*B*). Furthermore, the median anti-S IgG titers among HSCT patients stratified by concurrent receipt of high-dose steroid, tacrolimus, anti-CD20 therapy, and type of transplant are shown in Figure 2. Of these, patients who had concurrent anti-CD20 therapy had the lowest antibody titers. More descriptive analysis comparing the median anti-S IgG titers of other subgroups can be found in the Supplementary Data. Eleven (7.2%) HSCT recipients could not mount a positive response, regardless of the number of vaccines received. Of these nonresponders, 4 (27.3%) received 2 doses of the vaccine and 7 (72.7%) received 3 doses.

Autologous and Allogeneic Transplant Recipients

Autologous transplant patients had a median (IQR) anti-S IgG of 2303.5 (25.3–2500) U/mL measured at a median time (IQR) of 132 (83–181) days from the last vaccine dose. Allogeneic transplant patients had a median anti-S IgG (IQR) of 2500 (25.3–2500) U/mL at a median time (IQR) of 63 (36–145) days from the last vaccine dose (Supplementary Table 6).

Patients who had concurrent treatments for acute GVHD with tacrolimus had a median anti-S IgG (IQR) of 156.7 (3.53–1556) U/mL at a median time (IQR) of 107 (50–148) days from the last vaccine dose. Those who did not have tacrolimus treatment had a higher median anti-S IgG (IQR) of 2500 (153.5–2500) U/mL at a median time (IQR) of 80.5 (153.5–2500) days from the last vaccine dose (Supplementary Table 7).

HSCT Recipients Aged <65 vs ≥65 Years

Patients aged 65 years and older had a lower median anti-S IgG (IQR) of 1786 (62–2500) U/mL at a median time (IQR) of 84 (49–148) days from the last vaccine dose. Patients aged <65 years had a higher median titer (IQR) of 2500 (249.8–2500) U/mL at a median time (IQR) of 63 (34–154) days from the last vaccine dose.

Correlates of Seropositivity (Multivariable Analysis)

The results of the multivariable linear regression analysis indicated a positive correlation between the number of vaccine doses received and the quantitative anti-S IgG titer (Table 2). Specifically, as the number of doses increased, the anti-S IgG titer also increased correspondingly (coeff, 205; 95% CI, 30.1 to 381.5; $P = .022$). Being female (coeff, 343.5; 95% CI, −682.6 to −4.4; $P = .047$) was also associated with having a higher anti-S IgG titer compared with being male. Being age <65 years had a positive correlation with the quantitative anti-S IgG titer when compared with those aged 65 years or older (coeff, 365.2; 95% CI, −711.3 to −19.1; $P = .039$). Patients on concurrent anti-CD20 therapy had a statistically significant negative correlation with the quantitative anti-S IgG titer when compared with those who were not receiving the therapy (coeff, −1163.7; 95% CI, −1717.7 to −609.7; $P = .001$) (Table 2). The results of the regression analysis indicated that being on treatment for acute GVHD with steroids and tacrolimus and having chronic GVHD did not have a significant effect on the quantitative anti-S IgG titer (Table 2).

Additionally, receiving anti-CD20 therapy and being male were significantly associated with not mounting a positive vaccine response (OR, 0.16; 95% CI, 0.03 to 0.70; $P = .016$; and OR,

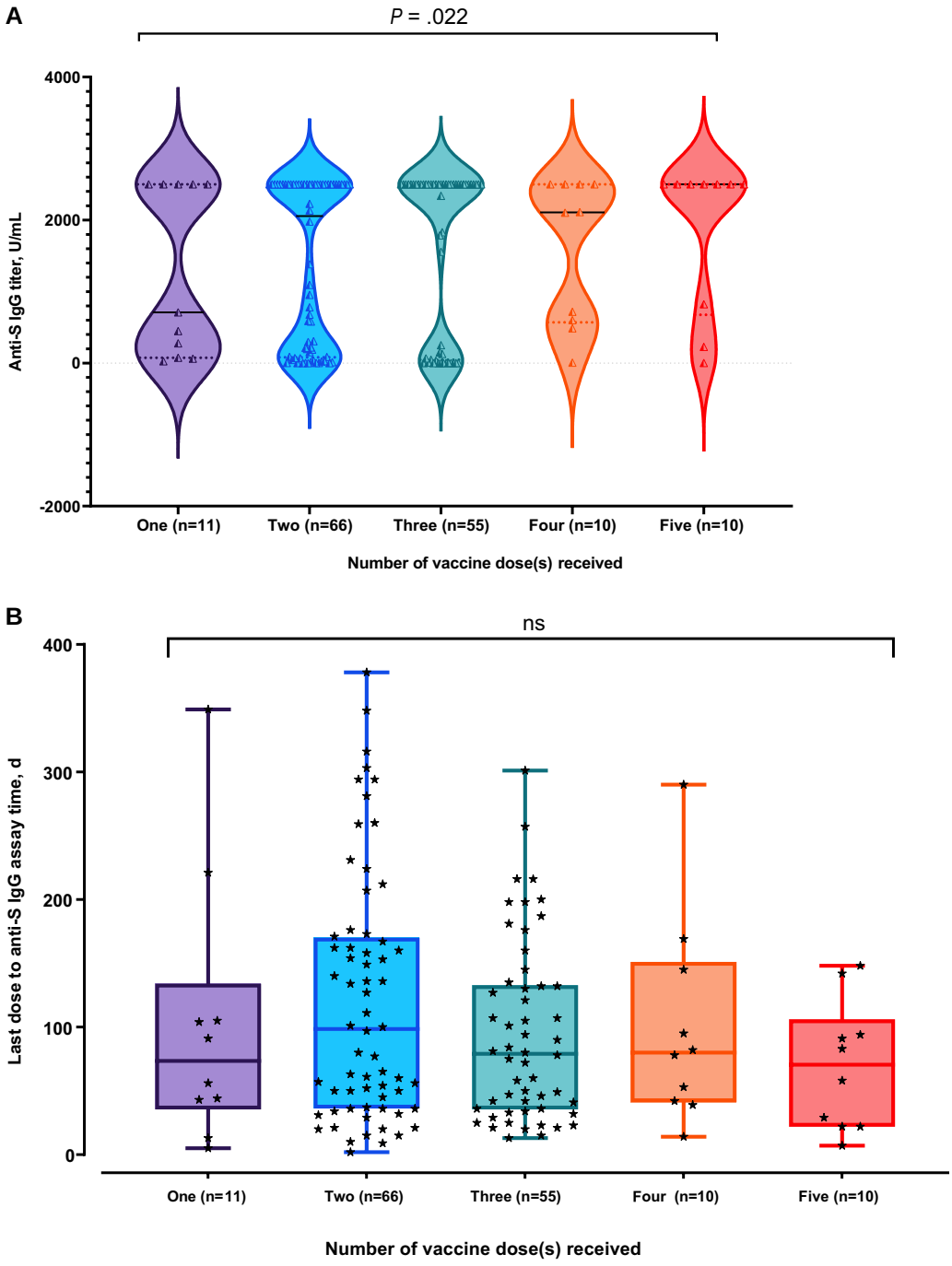

Figure 1. Anti-SARS-CoV-2 spike antibody titers among HSCT recipients. The result of the multivariate analysis shows an association between the number of vaccine doses received and the magnitude of anti-S IgG response. *A*, Anti-spike IgG responses on the y-axis and the number of vaccine doses received on the x-axis. *B*, The corresponding median time between anti-S IgG assay and the last dose received. A Mann-Whitney *U* test shows no significant difference in the last dose to assay time between the various dose categories. Abbreviations: HSCT, hematopoietic stem cell transplant; IgG, immunoglobulin G; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

0.11; 95% CI, 0.01 to 0.93; $P = .04$, respectively). Other factors, such as the number of doses, age, treatment of acute GVHD using systemic steroids or tacrolimus, and the presence of chronic GVHD, were not found to be statistically significant (Table 2).

DISCUSSION

Our results demonstrated that HSCT recipients had overall high seropositivity rates, defined as having detectable anti-S IgG titers, but the quantitative median anti-S IgG titers were

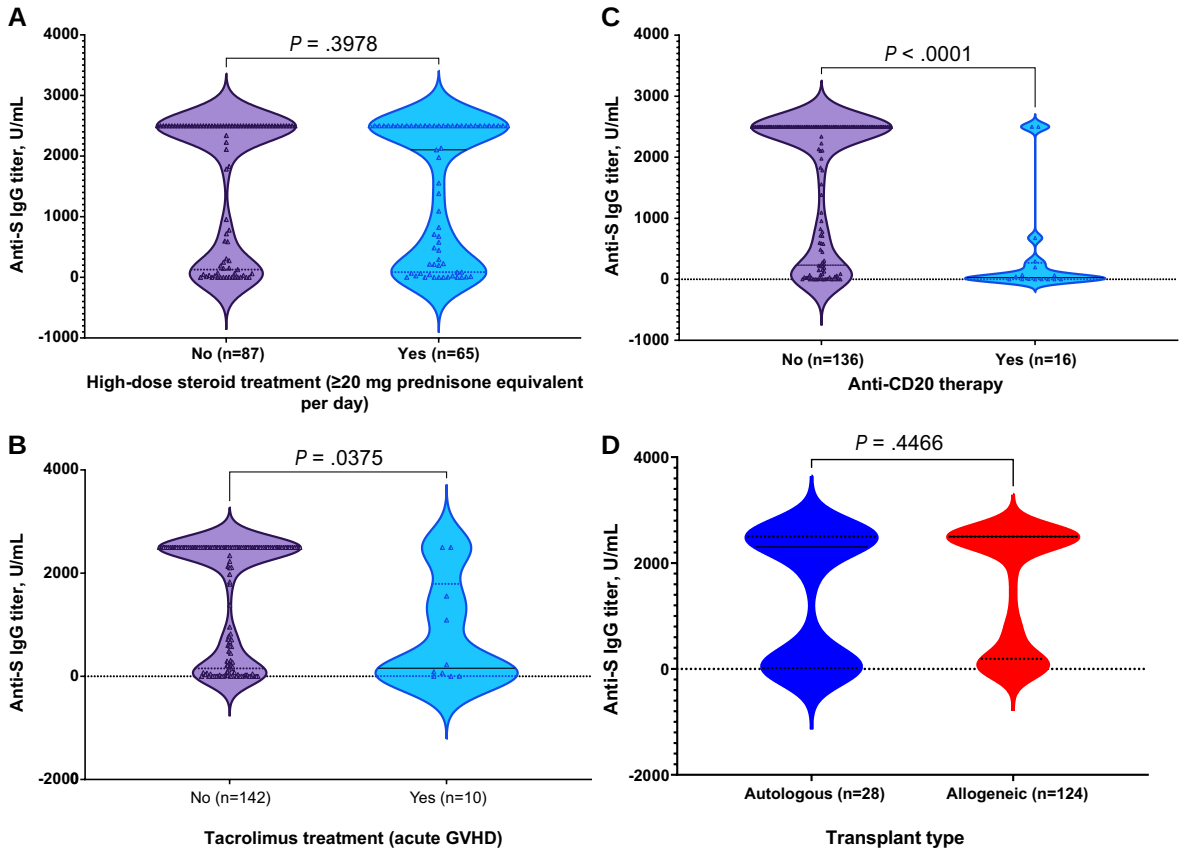

Figure 2. Anti-S IgG responses among various categories of HSCT recipients. Titers were compared between patients who were on concurrent immunosuppression therapy vs those who were not. *A*, High-dose (≥20 mg prednisone equivalent per day) steroid treatment. *B*, Tacrolimus treatment. *C*, Anti-CD20 monoclonal antibody treatment. *D*, Autologous HSCT vs allogeneic HSCT. All panels show a Mann-Whitney *U* test unadjusted analysis between the groups. Abbreviations: HSCT, hematopoietic stem cell transplant; IgG, immunoglobulin G; S, spike.

generally lower than reported among healthy participants who received COVID vaccines which were granted EUAs [20, 21]. In the phase 3 registrational studies, healthy adults had almost a 100% seropositivity rate and high quantitative titers after the first dose of SARS-CoV-2 vaccines [11, 22]. While antibody levels are a clear correlate of protection against SARS-CoV-2 infection, there are likely other mechanisms of protection [1, 23–28]. Therefore, the results of the quantitative anti-S IgG titers and seropositivity in particular must be interpreted with caution and should not be taken as the sole indicator of immune-protectiveness among HSCT recipients.

Our results depicted that the use of anti-CD20 therapy was associated with being a non-responder and having significantly lower anti-S IgG titers. This supports previous findings in the literature that anti-CD20 therapies inhibit B-cell antibody production and deplete peripheral B cells, leading to a decrease in vaccine-elicited IgG titers [22–24]. To ensure that HSCT recipients benefit optimally from SARS-CoV-2 vaccination, it may be important to consider the timing of vaccine administration in regards to anti-CD20 therapy if feasible. Furthermore, clinicians should be aware that these patients remain at risk despite vaccination and should be counseled on the need for additional layers of protection known to supplement vaccination and reduce transmissibility of SARS-CoV-2 infection as recommended by the US Centers for Disease Control and Prevention (CDC) [29].

This study found no significant difference in the response to SARS-CoV-2 vaccines between HSCT recipients receiving concurrent GVHD treatment (tacrolimus, steroids) and those not receiving treatment, after adjusting for confounding factors. However, another study showed that ongoing GVHD and treatment negatively impact the anti-S IgG response in HSCT recipients compared with healthy adults [30, 31]. One study among Japanese patients showed that allogeneic transplant patients, some of whom had treatment for GVHD, showed a better overall anti-S IgG response compared with autologous transplant patients in the cohort [32].

Immunosuppression in other contexts has also been found to lead to blunted vaccine-elicited immune responses. In a recent prospective study, Griessbach and colleagues offered a third dose of either the Moderna or Pfizer/BioNTech SARS-CoV-2 vaccine to a cohort of patients either living with HIV or who had had kidney or lung transplants [33]. They

Table 2. Linear and Logistic Regression Table

Table of Linear Regression Analysis				
	Univariable Analysis		Multivariable Analysis	
	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
Doses of vaccine received	154.20 (−35.36 to 343.77)	.110	205.79 (30.10 to 381.47)	**.022**
Age				
≥65 y	−293.60 (−664.22 to 77.03)	.120	−365.20 (−711.32 to 19.09)	**.039**
<65 y (ref.)				
Sex				
Male	−451.00 (−808.98 to −92.99)	**.014**	−343.51 (−682.58 to 4.45)	**.047**
Female (ref.)				
Anti-CD_{20} therapy				
Yes	−1256.10 (−1813.74 to −698.45)	**.000**	−1163.67 (−1717.69 to −609.66)	**.000**
No (ref.)				
Systemic corticosteroids				
Yes	−157.58 (−524.75 to 209.59)	.398	−28.21 (−399.54 to 343.13)	.881
No (ref.)				
Acute GVHD treatment (tacrolimus)				
Yes	−769.09 (−1493.01 to −45.17)	**.037**	−531.75 (−1212.76 to 149.26)	.125
No (ref.)				
Chronic GVHD				
Yes	200.31 (−174.42 to 575.03)	.293	242.66 (−128.21 to 613.53)	.198
No (ref.)				
Table of Logistic Regression Analysis				
	Univariable Analysis		Multivariable Analysis	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Doses of vaccine received	0.98 (0.52 to 1.86)	.948	1.16 (0.59 to 2.31)	.664
Age				
≥65 y	0.74 (0.22 to 2.56)	.640	0.58 (0.15 to 2.26)	.436
<65 y (ref.)				
Sex				
Male	0.10 (0.01 to 0.84)	**.033**	0.11 (0.01 to 0.93)	**.042**
Female (ref.)				
Anti-CD_{20} therapy				
Yes	0.16 (0.04 to 0.64)	**.009**	0.16 (0.03 to 0.70)	**.016**
No (ref.)				
Systemic corticosteroids				
Yes	0.89 (0.26 to 3.05)	.851	1.75 (0.38 to 8.01)	.472
No (ref.)				
Acute GVHD treatment (tacrolimus)				
Yes	0.68 (0.08 to 5.93)	.729	1.20 (0.12 to 11.69)	.878
No (ref.)				
Chronic GVHD				
Yes	0.70 (0.20 to 2.41)	.573	0.45 (0.10 to 2.09)	.311
No (ref.)				

P values ≤ .05 are indicated in boldface.

Abbreviation: GVHD, graft-vs-host disease.

found that while the majority of participants had a serologic response, the response rate was higher among persons with HIV compared with solid organ transplant recipients (100% vs 73% using the same cutoff value as we used for the Roche Elecsys assay) [33]. Further research is needed to fully elucidate the complex relationship between GVHD, immunosuppressive medications, and vaccine efficacy in HSCT patients.

Patients who received a higher number of SARS-CoV-2 vaccinations had a significantly higher quantitative anti-S IgG response. This result is consistent with other studies among healthy individuals and HSCT recipients [14, 34]. These data, therefore, generally support the recommendation for booster doses as recommended by the CDC [29], particularly for transplant patients who have lower antibody levels and are more

vulnerable to severe illness [12]. However, the optimal timing of booster doses should be further explored in future prospective studies.

Our results show that women had a significantly higher anti-S antibody level compared with men, consistent with other reports in healthy individuals [30, 35]. Ongoing research suggests that hormones such as estrogen may have an immunomodulatory function [36]. Environmental and genetic factors may also play a role [37]. Further studies are needed to elucidate the underlying mechanisms.

Additionally, being age <65 years was associated with a stronger quantitative antibody response compared with older patients age ≥65. This observation is consistent with what has been described in other studies among allogeneic HSCT recipients and healthy participants who had SARS-CoV-2 vaccinations [2, 38, 39]. While an age-related decline in immune responses, known as immunosenescence, has been observed in older individuals compared with their younger counterparts [40–42], the mechanisms underlying this phenomenon are an area of active research [43–45].

Our study has several limitations that should be taken into account when interpreting the findings. The study was conducted retrospectively, meaning that a causal relationship cannot be established from the results. Additionally, the clinical significance of the findings remains unknown, as correlates of protection may vary between immunocompromised hosts and healthy clinical trial participants. It is also worth noting that our study participants had not had variant-containing bivalent booster vaccines during the observation period, and treatment records were censored on the date of a positive SARS-CoV-2 infection. In addition, circulating viral variants complicate the correlates analyses. The study's population was predominantly White, limiting the generalizability of the findings to other racial or ethnic groups. Furthermore, only a small proportion of the sampled population had the complete vaccine series and serial anti-S IgG titer measurements, which prevented us from assessing vaccination responses longitudinally. Moreover, while the heterogeneity of vaccine types may have influenced the results, most patients received mRNA vaccines. The study also did not consider the duration of prophylaxis or treatment against GVHD, only whether recipients had treatment or not. Lastly, the results of this study may be challenging to compare with other studies that used different antibody assay techniques, as the reference range and assay limits may vary. These limitations indicate the need for larger prospective studies to confirm the results and gain a better understanding of the optimal vaccination strategy for HSCT patients.

CONCLUSIONS

The FDA-authorized SARS-CoV-2 vaccine series produced an immunogenic response among the majority of HSCT patients, but the response was suboptimal for certain subsets of the cohort, such as older patients and those who had received anti-CD20 therapy. The number of vaccine doses administered correlated with the magnitude of the anti-S IgG response, and quantitative anti-S IgG assays could therefore be conducted for early identification of patients who fail to respond to vaccination. The findings support the current recommendations for HSCT patients to receive a 3-dose primary series followed by serial booster COVID vaccines to optimize protection against SARS-CoV-2 infection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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